

BnAb Approaches to HIV Cure

Lessons learned – promising strategies – key challenges



HIV Cure Workshop

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July 30, 2025**



HIV cure research – mechanisms + interventions

Dynamics of Persistence in PWH on ART

- IPDA, VOA, single cell, flow
- Struggle between immune selection, clonal expansion, immune exhaustion

Mechanisms of natural control – EC, PTC, PIC

- Distinct mechanisms of control between
- Immune selection: innate, adaptive humoral and cellular

Combination immunotherapy

- **BnAbs have been foundational**
- + cytokines, LRA, vaccine, etc
- Signal: increased frequency of durable PIC

Cell and gene therapy

- **BnAbs are a component** –via vectored or cellular delivery
- Proviral excision, engineered cells, vectored delivery

HIV bnAbs for cure interventions

Safe, tolerable, desirable PK

- Without AE from small molecule ART
- Long-acting via LS mutation
- Tail: challenges and opportunities

Antiviral activity

Virus suppression + allow time for immune system

- Resistance – limitation, challenge of screening reservoir
- Now, increasing breadth and potency
 - Pipeline development key

Effector function

Reservoir reduction clearance

- Proof in vitro, other pathogens
- Fc enhancement, combination therapy
- Clinical trial demonstration needed

Vaccinal effect

Enhancement of HIV-specific immunity

- Proof in other pathogens, signals in HIV
- Clinical trial demonstration, defined mechanisms and outcomes needed

Approaches and required mechanisms

- **bnAbs+ at ART initiation**

- Limit reservoir formation, enhance HIV-specific immunity to control virus
- requirements: broad binding, effector function, vaccinal effect

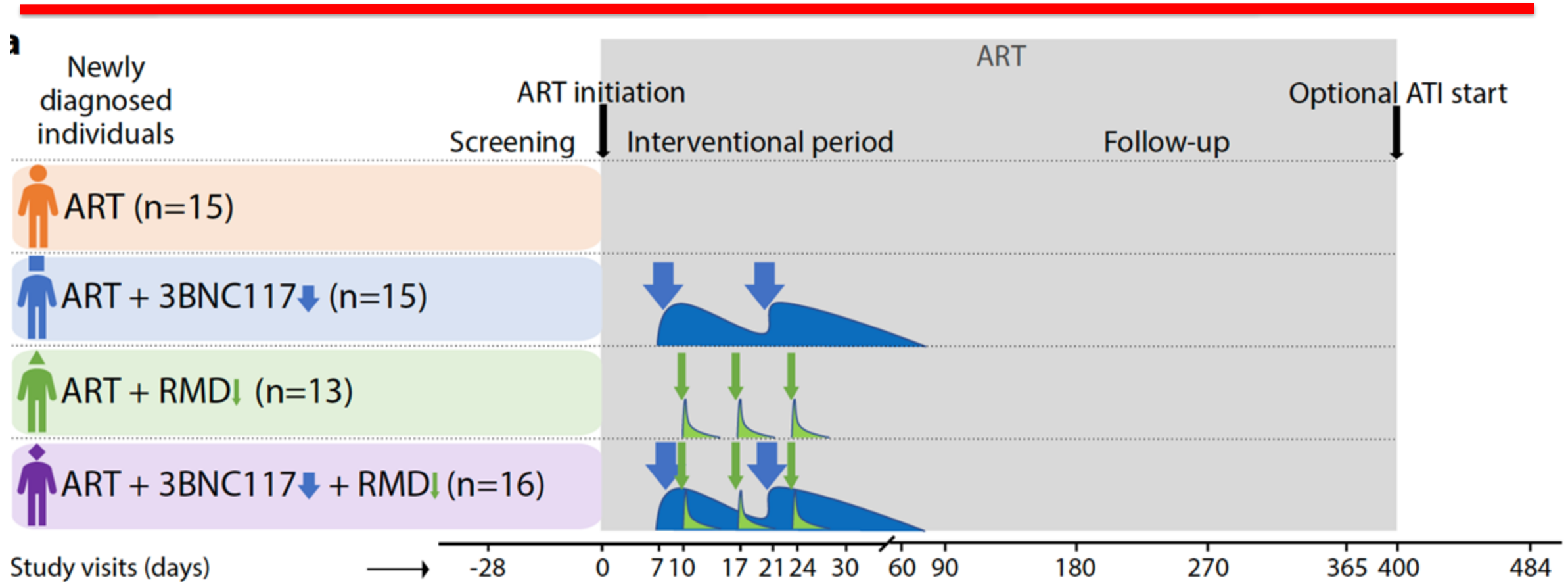
- **bnAbs+ at ATI**

- Suppress virus and allow time for enhanced HIV-specific immunity
- requirements: broad binding and neutralization >> effector function, vaccinal effect

- **bnAbs+ during ART**

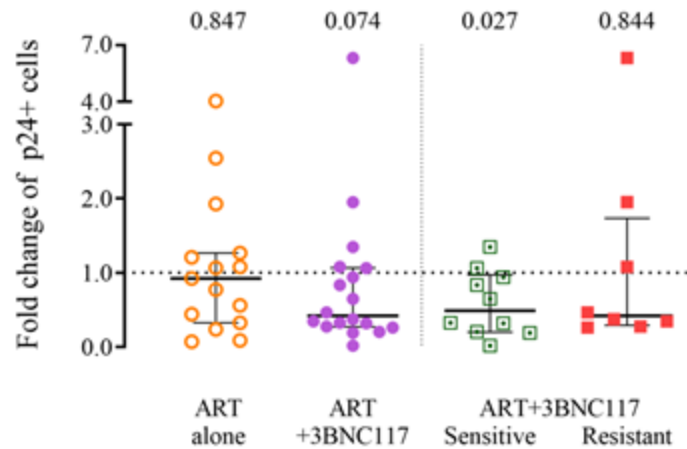
- Reduce □ clear reservoir, enhance HIV-specific immunity
- requirements: broad binding, effector function, vaccinal effect
- ****bnAb or anAb-boosting therapeutic vaccines****

eCLEAR: bnAb+ at ART initiation

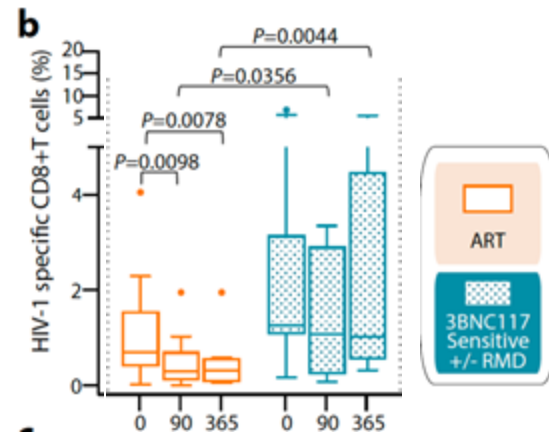


- Hypothesis: interventions at ART initiation limit formation of the reservoir + enhance vaccinal effect

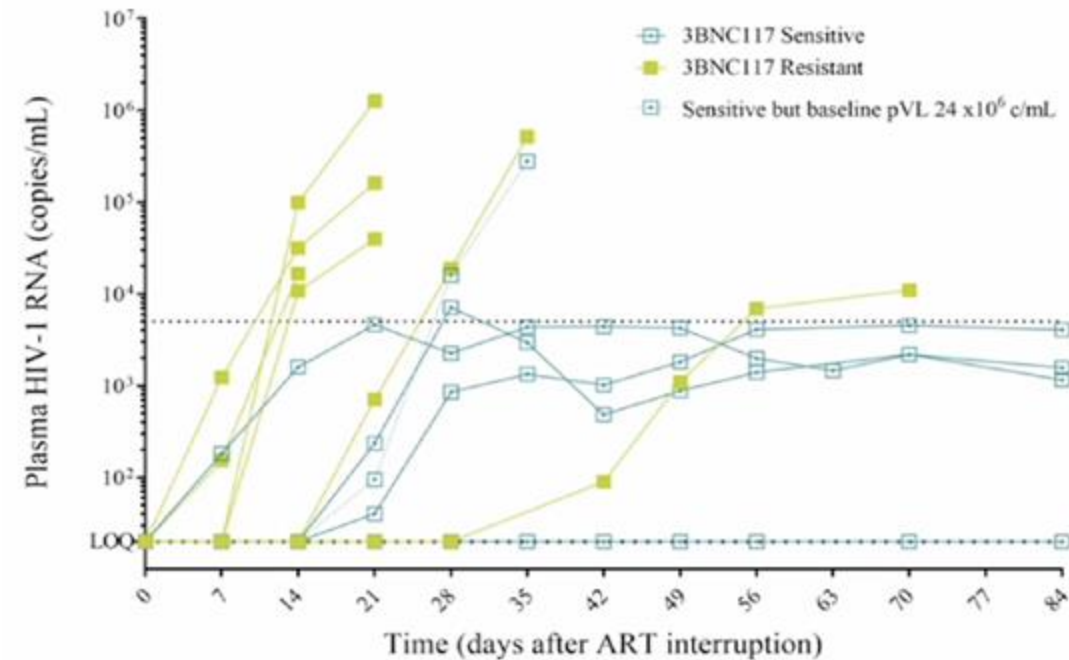
eCLEAR: HIV+ cell clearance, immunity, control



Faster decline in viremia; decrease p24+ cells



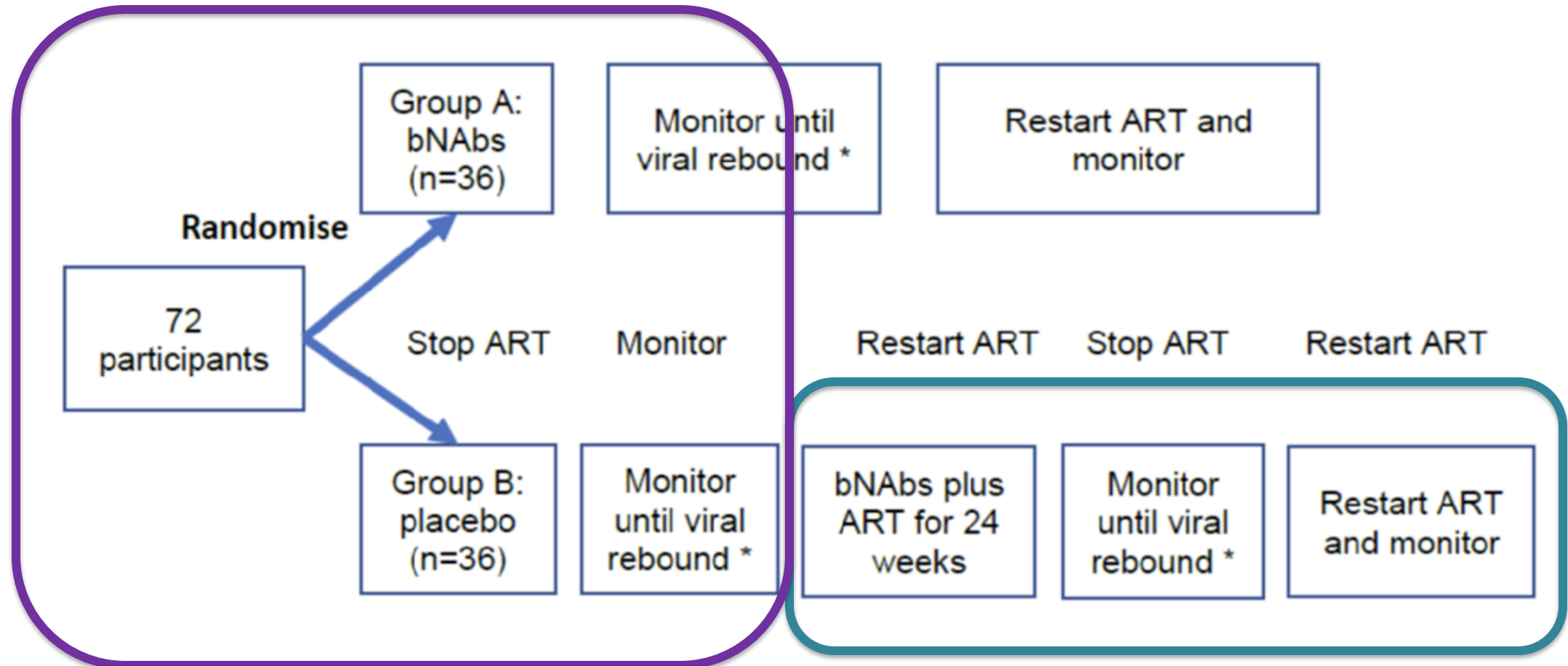
Higher frequency & greater IFN responses of Gag-specific CD8 T cells



Enhanced virus control, delay ART re-initiation in bnAb-treated w sensitive reservoirs

- Multiple ongoing trials of bnAbs at ARTi, eg, RIO, A5388, A5417

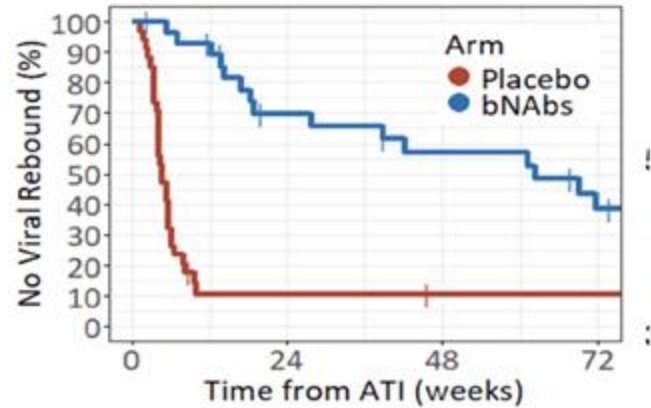
RIO: bnAbs at early ART initiation



Preliminary Results on Stage 1

Placebo recipients receive delayed intervention

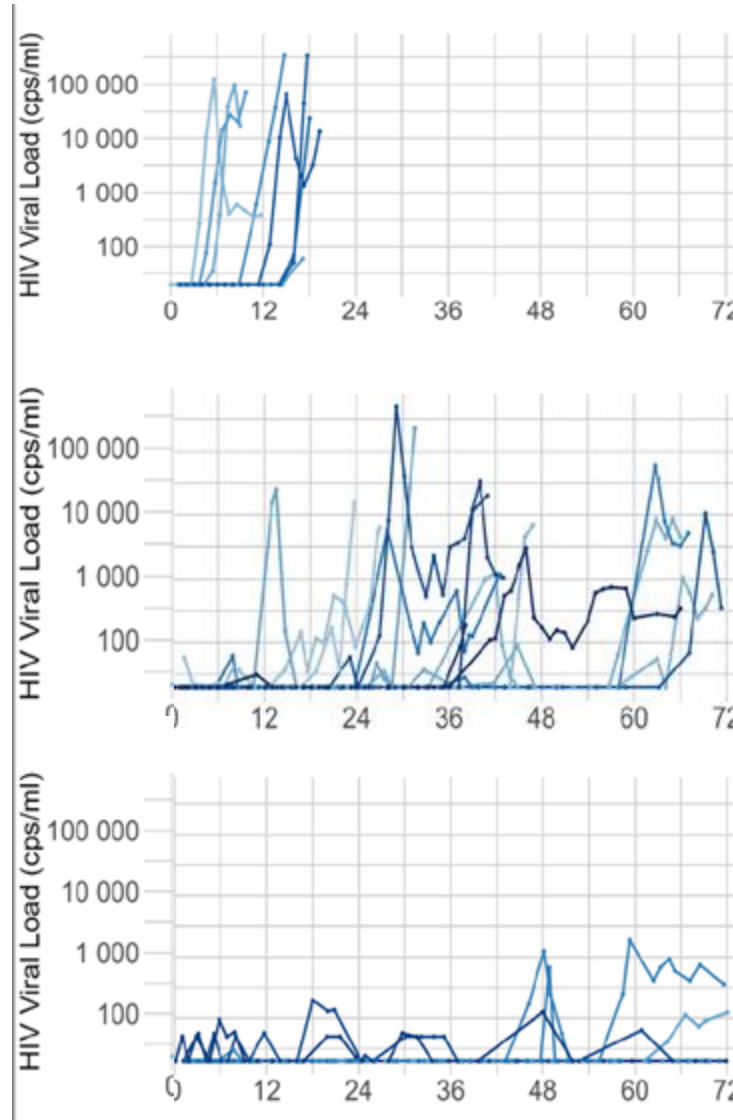
RIO: delayed rebound with bnAbs & post-bnAb



Number of participants

	0	24	48	72
bnAbs	34	20	13	8
placebo	34	3	2	2

- **Week 20:** 75% vs 9% rebound
 - HR 0.09, 95% CI (0.04, 0.21)
- **Week 72:** 39% vs 6% rebound
 - HR 0.24 (0.13, 0.44)
- **Potential mechanisms:** early ART, long bnAb tail allowing immunity, vaccinal effect



Rapid rebound (n=8)

- through high bnAb
- 4/8 with resistance

Delayed rebound (n=14)

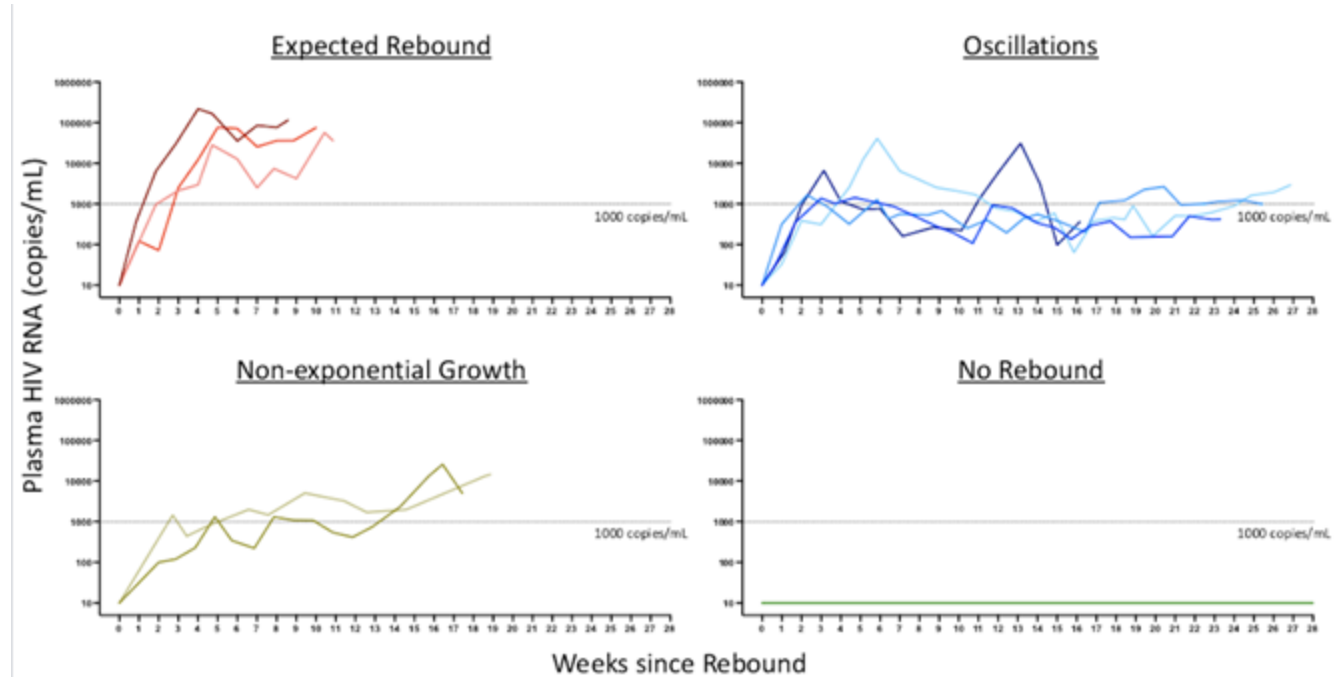
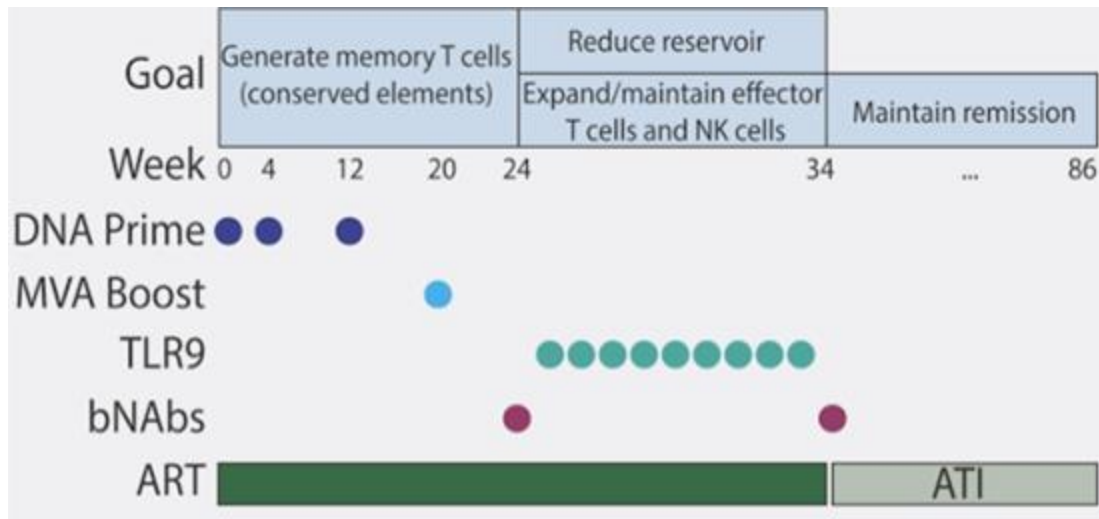
- through waning bnAb

Viral control (n=8)

- rebound post-bnAb

UCSF/amfAR study — preliminary results

Study Schema

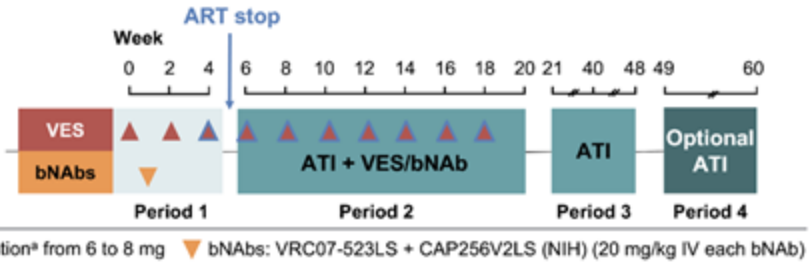


- Single arm, proof of concept study of **2 bnAbs on ART and at ATI + T cell vaccine**, + **TLR9 Agonist**
- Preliminary results suggest distinct viral rebound kinetics
 - expected, oscillations and non-exponential growth, post-intervention control
- **Potential mechanisms:** long bnAb tail allowing immunity time, vaccinal effect, reservoir reduction, vaccine/TLR9 immunity

FRESH: bnAbs+ in acute ART-treated RSA women

FRESH: bnAbs + TLR7 after hyperacute ART in RSA Women

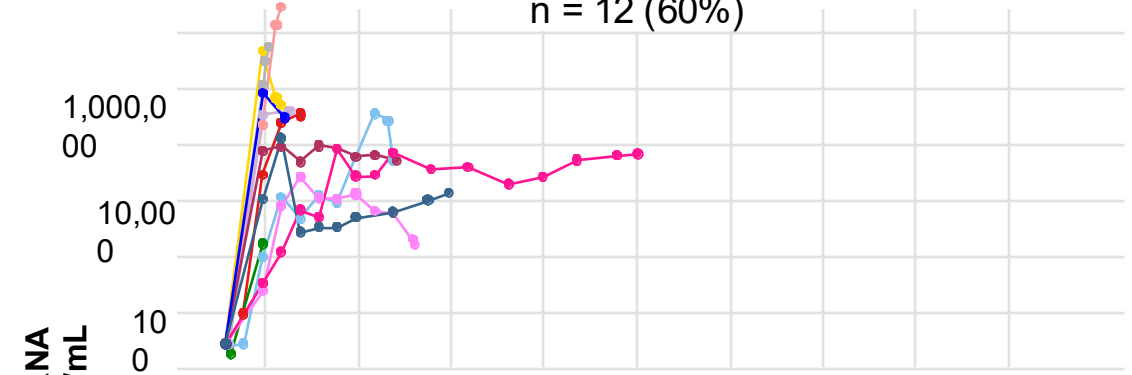
- FRESH cohort: S. African women with very early ART initiation
- Virally suppressed on ART > 12 months, high CD4
- Sensitive to at least 1 of the 2 bnAbs



- **Delay, distinct pattern of rebound vs. chronic-ART historical controls**
 - The median time to rebound: 11 weeks (95% CI, 7-18)
 - 12 (60%) participants exhibited typical viral rebound dynamics; 8 (40%) participants exhibited oscillation and nonexponential growth
- **Potential mechanisms:** early ART, long bnAb tail allowing immunity time, vaccinal effect

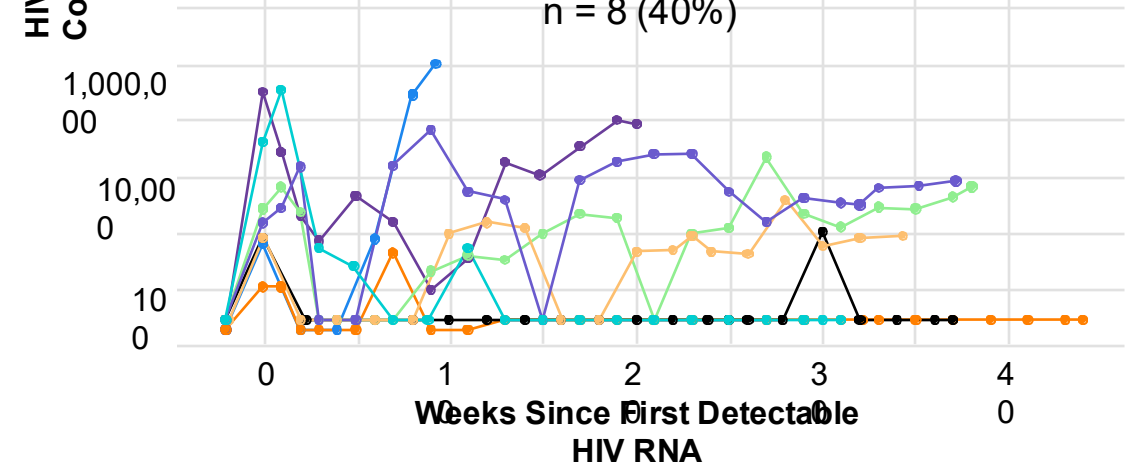
Typical Rebound Dynamics

n = 12 (60%)

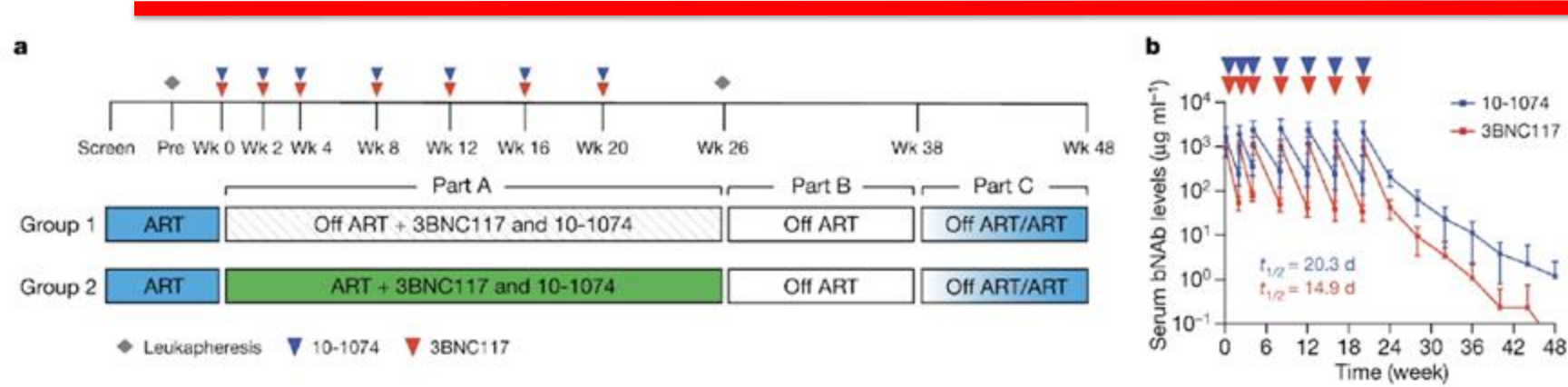


Oscillating Viral Rebound Dynamics and Control

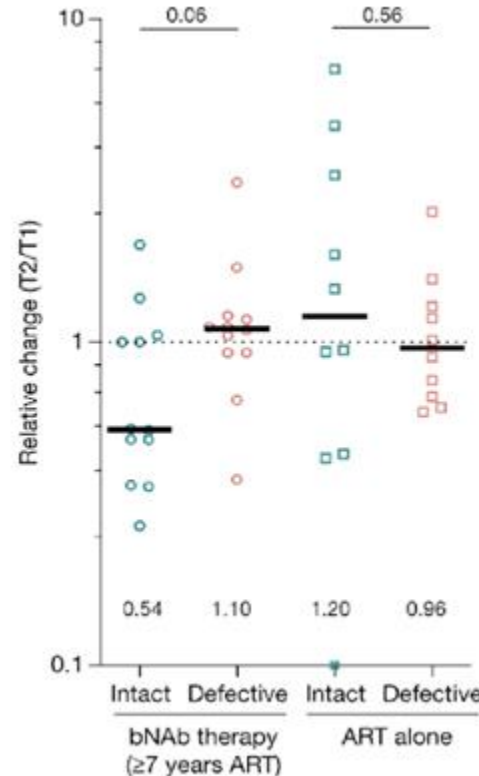
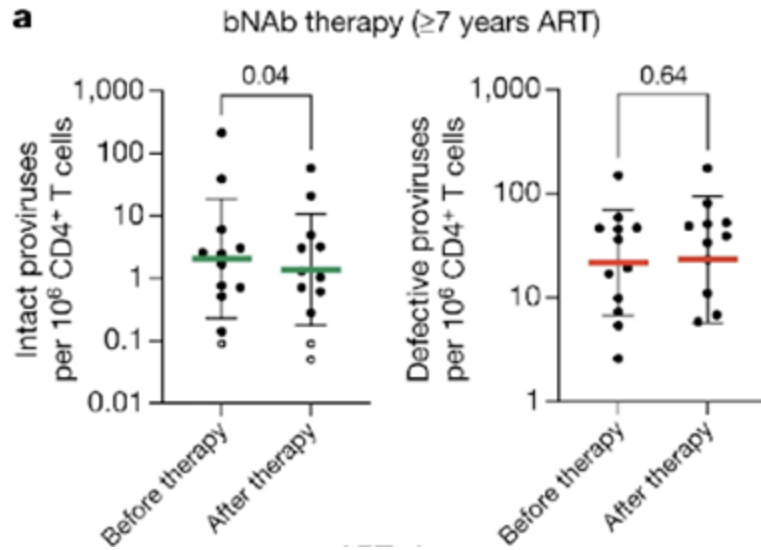
n = 8 (40%)



BnAbs on ART (low antigen)



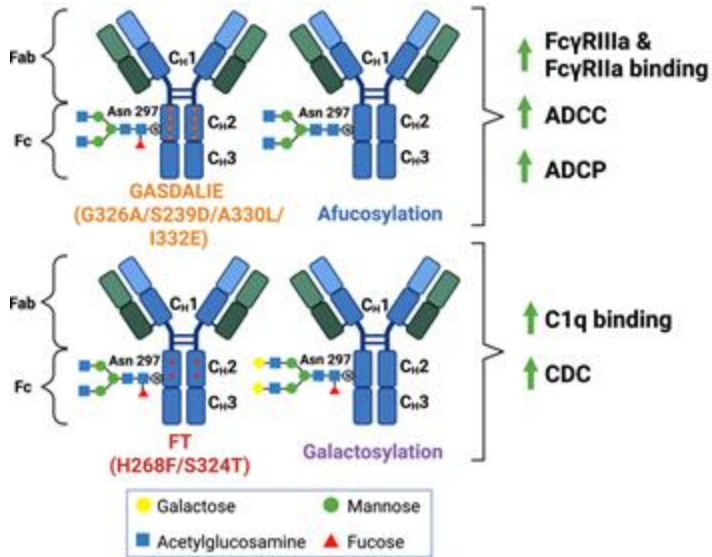
- Durable suppression of sensitive reservoirs
- Modest reservoir reduction on ART or with virus suppression



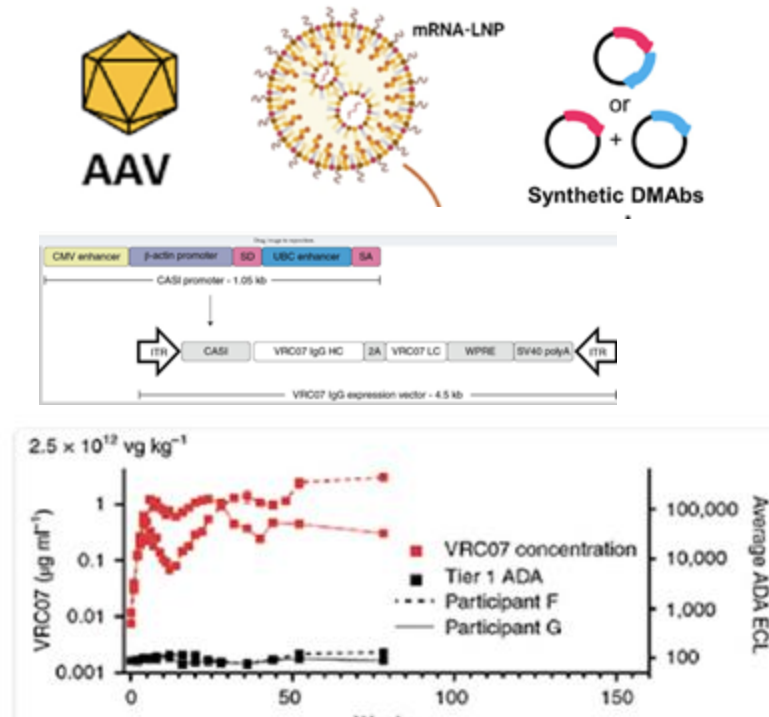
- Lenacapavir + 2 bnAbs (LEN + ZAP + MAP): durable suppression, but no HIV-specific CD8 T cell enhancement

0.54-fold reduction (p=0.04) in intact reservoir in PWH (>7yr ART) after 26 weeks bnAb

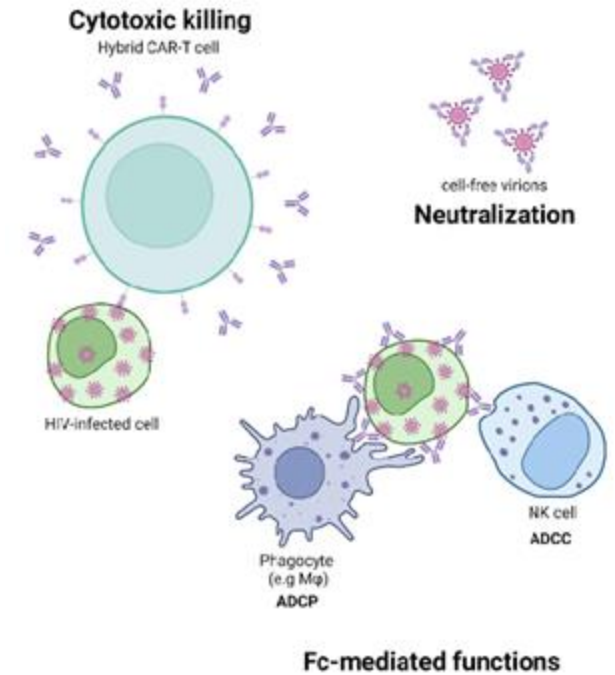
Technological Advances



Fc modifications
 Enhanced half-life, effector-function, IC formation



Targeted, vectored-delivery bnAbs
 AAV, mRNA-LNP, DNA



Combinations:
CAR-T cells secreting bnAbs
 Stylianidou, Vanderkherkhove, IAS 2025

Challenges + Opportunities

- **Combination immunotherapy**
 - Promising signals
 - Complex, burdensome clinical trials. Challenging to delineate mechanism, advance specific components. *Can we simplify trials and isolate effective interventions?*
- **BnAbs at ART initiation; after early ART**
 - Promising signals
 - Not directly relevant to >36M PWH on chronic-initiated ART. *Can we iterate from mechanisms to larger population?*
- **Cure-specific mechanisms**
 - Effector function and vaccinal effect hold great potential
 - Not consistently demonstrated in HIV cure studies. *Can we demonstrate outcome in feasible clinical juncture and mechanism in human studies?*
- **Therapeutic vaccine – bnAb or anAb enhancing**
 - Early clinical trials
 - Inform prevention or have benefit for PWH on ART. *Can we show benefit in PWH?*
- **Enhanced, delivered bnAbs**
 - Antibody engineering and gene therapy rapidly advancing
 - Challenging to rapidly test safety, efficacy

Thank you!

